Pharmacy Update
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SPECIAL ISSUE

Zoledronic Acid for Injection (ZOMETA™)

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Indications

Zoledronic acid monohydrate is indicated for the treatment of hypercalcemia of malignancy and for treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors (in conjunction with standard antineoplastic therapy).[1] Table 1 summarizes the FDA-approved indications for pamidronate and zoledronic acid.

Table 1: FDA-approved Indications for Pamidronate and Zoledronic Acid[1,2]

Indication	Pamidronate	Zoledronic Acid
Paget's disease	X	
Treatment of hypercalcemia of malignancy	X	X
Osteolytic bone metastases of solid tumors and osteolytic lesions of multiple myeloma	X	X

Clinical Pharmacology

Zoledronic acid is a bisphosphonic acid. Like other bisphosphonates, it inhibits osteoclast formation, osteoblast proliferation, and DNA synthesis.[3] Zoledronic acid is a more potent inhibitor of bone resorption than risedronate, alendronate, pamidronate, or etidronate. Zoledronic acid is 100 to 850 times more potent than pamidronate.[3-6] It has minimal effects on skeletal mineralization. [3] In long-term animal osteoporosis models, zoledronic prevented time- and dose-dependent bone loss in the total body, lumbar spine, and femur and was associated with increases in bone mass at those sites. Trabecular deterioration was also prevented.[3] In animal models of bone metastases, zoledronic acid prevented destruction of trabecular bone, reduced tumor volume in bone, and increased tumor cell apoptosis in bone metastases secondary to osteoclast inhibition or a direct effect associated with the high concentration in bone.[7,8] Zoledronic acid can inhibit breast and prostate carcinoma cell invasion, an early step in bone metastases.[8]

Zoledronic acid, like other bisphosphonates, has also recently been recognized to have broader direct antitumor effects. Zoledronic acid has been demonstrated to inhibit cell growth and induce apoptosis in human myeloma, breast cancer, and prostate cancer cell lines.[9-13] In breast cancer cell lines, zoledronic acid demonstrated synergistic activity with paclitaxel and tamoxifen.[11,13] Zoledronic acid also appears to inhibit proliferation and induce apoptosis in human endothelial cells *in vitro* and to inhibit an angiogenic response *in vivo*.[14]

Zoledronic acid has also been demonstrated to decrease type II collagen degradation, suggesting it may have chondroprotective effects.[15] It has also been demonstrated to preserve cortical bone integrity in inflammatory arthritis.[16]

Pharmacokinetics

Zoledronic acid plasma concentrations are dose proportional.[17]

Although plasma concentrations fall to less than 1% of the concentration at the end of the infusion by 24 hours, zoledronic acid remains detectable to day 29 after administration.[17] Elimination is triphasic, with an alpha half-life of 0.23 hours, a beta half-life of 1.75 hours, and a terminal elimination half-life of 167 hours.

Zoledronic acid is quickly taken up into the bone, then slowly released.[17] It is only approximately 22% plasma protein bound.[1]

Zoledronic acid does not undergo biotransformation *in vivo*; it is primarily eliminated intact via the kidney.[1] Clearance correlates with renal function in patients with normal to moderately impaired renal function. Clearance does not appear to be influenced by body weight, body mass index, gender, age, or race (Caucasian, Black, or Oriental), and is independent of the dose.[1,17] Pharmacokinetics have not been evaluated in patients with hepatic impairment or severe renal impairment.[1]

See Table 2 for a comparison of the pharmacokinetics of pamidronate and zoledronic acid.

Table 2: Comparison of the Pharmacokinetics of Pamidronate and Zoledronic Acid[1,2]

Pharmacokinetic Parameter	Pamidronate	Zoledronic Acid
Half-life	28 hours	167 hours
Clearance	107 mL/min	93 mL/min
Renal elimination	Extensive	Extensive

Comparative Efficacy

Hypercalcemia of Malignancy

A pooled analysis was performed on two identical, concurrent, double-blind trials comparing zoledronic acid and pamidronate in the treatment of hypercalcemia of malignancy. Patients with moderate-to-severe hypercalcemia (corrected serum calcium ≥3 mmol/L or 12 mg/dL) were treated with a single dose of zoledronic acid 4 mg or 8 mg as an infusion over 5 minutes or pamidronate 90 mg as an infusion over 2 hours. All patients also were given 250 mL intravenously prior to the infusion of the study medication and continued to receive intravenous fluids for 4 hours. Blood was drawn for serum chemistry including corrected serum calcium on days 4, 7, 10, 14, 17, 21, 24, 28, and weekly thereafter up to day 56. Patients were followed for 56 days or until relapse (corrected serum calcium ≥2.9 mmol or 11.6 mg/dL). If the corrected serum calcium was not lower than baseline by at least 0.05 mmol/L (0.2 mg/dL) on day 4 or 0.25 mmol/L (1 mg/dL) on day 7, or was ≥2.9 mmol/L (11.6 mg/dL) on day 10, then re-treatment with zoledronic acid 8 mg was initiated for refractory disease. Safety was assessed in 287 patients, efficacy in 275. A complete response (normalization of corrected serum calcium to ≤2.7 mmol/L or 10.8 mg/dL) by day 10 was achieved in 88.4% of patients treated with zoledronic acid 4 mg (p=0.002), 86.7% treated with zoledronic acid 8 mg (p=0.015), and 69.7% treated with pamidronate. Normalization of corrected serum calcium by day 4 occurred in 55.6% of patients treated with zoledronic acid 8 mg and 33.3% of patients treated with pamidronate (p=0.021). Zoledronic acid 4 mg was associated with normalization of corrected serum calcium by day 4 in 45.3% of patients. Rates of complete response in the zoledronic acid groups were similar regardless of whether patients had bone metastases; in the pamidronate group, a complete response by day 10 was achieved in 80% of patients with bone metastases, but only 61% of patients without bone metastases. The median duration of complete response was 32 days with zoledronic acid 4 mg, 43 days with zoledronic acid 8 mg, and 18 days with pamidronate. Seventy patients who relapsed or were refractory to the initial dose, received an 8 mg dose of zoledronic acid. Efficacy was assessed in 69 patients. Mean corrected serum calcium levels dropped from 3.17 mmol/L before re-treatment to 2.71 mmol/L at day 10. A complete response was achieved in 36 patients (52%) by day 10.[6,18]

Zoledronic acid was evaluated in a dose-finding study enrolling 33 patients with hypercalcemia of malignancy. Doses administered were 0.002 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, and 0.04 mg/kg. Median infusion time was 30 minutes. The mean baseline calcium level was 3 mmol/L. Calcium levels normalized in five of five patients treated with zoledronic acid 0.02 mg/kg and 14 of 15 patients treated with zoledronic acid 0.04 mg/kg. At the highest dose, calcium levels normalized within 2 to 3 days of administration.[5]

Metastatic Bone Lesions

Zoledronic acid was compared with pamidronate in a double-blind study enrolling 280 patients with osteolytic metastatic lesions due to breast cancer or multiple myeloma. Patients received zoledronic acid 0.4 mg, 2 mg, or 4 mg as a 5-minute infusion, or pamidronate 90 mg as a 2-hour infusion. Doses were repeated every 4 weeks for up to 10 months. The need for radiation therapy to bone was reduced with zoledronic acid 2 mg and 4 mg and with pamidronate 90 mg ($p<0.05$), but not with the lower zoledronic acid dose. Skeletal-related events, pathologic fractures, and hypercalcemia occurred less frequently among patients treated with zoledronic acid 2 mg or 4 mg or pamidronate, than among patients treated with the lower zoledronic acid dose. At least one skeletal-related event occurred in 35% of the patients in the zoledronic acid 2 mg group, 33% in the zoledronic acid 4 mg group, 30% in the pamidronate group, and 46% in the zoledronic acid 0.4 mg group. Lumbar spine bone mineral density was increased (6.2% to 9.6%) and N-telopeptide was reduced (-37.1% to -60.8%) in all groups. Performance status, pain scores, and analgesic scores did not differ between the groups.[19]

Continued administration of zoledronic acid beyond 2 years on a compassionate-use basis in 22 breast cancer patients treated with zoledronic acid (four patients) or pamidronate (18 patients) for 2 years in a clinical trial was described. Patients received pamidronate 90 mg or zoledronic acid 4 mg or 8 mg every 3 to 4 weeks. Follow-up in these patients ranged from 2.2 to 6 years (mean 3.6 years). Therapy remained effective in preventing skeletal events, with fractures occurring in 2 of 12 patients (16%) with a history of a skeletal event prior to therapy and 2 of 10 patients (20%) without a history of skeletal events prior to therapy. The fracture rate beyond 2 years of treatment was not greater than during the first 2 years.[20,21]

Efficacy was also reported in a double-blind, placebo-controlled study enrolling 422 patients with prostate cancer

and a history of metastatic bone disease. Patients received either zoledronic acid 4 mg as a 15-minute infusion every 3 weeks or placebo for a total of 15 months. By month 15, 33% of zoledronic acid-treated patients and 44% of placebo-treated patients had experienced a skeletal related event (p=0.021). Skeletal related events included pathological fractures, spinal cord compression/vertebral collapse, radiation for pain relief, and radiation to prevent pathologic fractures or spinal cord compression/collapse. The median time to first skeletal-related event was 321 days for the placebo group, but had not been reached in the zoledronic acid group at the time results were reported at an oncology meeting.[22]

Zoledronic acid and pamidronate are also being compared in an open-label study set to enroll 200 patients with metastatic bone disease due to breast cancer or multiple myeloma. Patients are receiving either zoledronic acid 8 mg or pamidronate 90 mg every 3 to 4 weeks for a maximum of six infusions. Preliminary results from 18 patients receiving a median of 2.3 infusions per patient have been presented. The bone metabolism parameters cross-linking N-telopeptide, bone-specific alkaline phosphatase, and free deoxypyridinoline were reduced to a greater extent in the zoledronic acid-treated patients.[23] Zoledronic acid 4 mg and pamidronate 90 mg are also being compared in an ongoing 12-month, double-blind study enrolling more than 1,600 patients with multiple myeloma or breast cancer with osteolytic lesions. A placebo-controlled study is also evaluating zoledronic acid 4 mg in patients with osteolytic lesions and tumors other than multiple myeloma, breast cancer, or prostate cancer.[24] Several large studies have also been proposed to assess the efficacy and tolerability of zoledronic acid in conjunction with standard adjuvant therapy in the prevention of disease recurrence in patients with node-positive breast cancer, prevention of bone metastases in breast cancer, and the prevention of bone metastases in prostate cancer.[24]

Zoledronic acid was also evaluated in a Phase I dose-finding study enrolling 59 patients with osteolytic bone metastases (36 patients with multiple myeloma, 17 with breast cancer, and 6 with other cancer types). Zoledronic acid was administered intravenously over 5 to 30 minutes monthly for 3 months at doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 1.5 mg, 2 mg, 4 mg, and 8 mg. The median percent reduction in urine calcium-creatinine ratio was 62.3% at the 2 mg dose. Greater reductions in urinary N-telopeptide were observed with doses of 0.8 mg or higher, and suppression of pyridinoline and deoxypyridinoline occurred most quickly with doses of 1.5 mg or higher. Pain scores, analgesic use, ECOG performance status, response of lytic lesions, and serum osteocalcin levels did not show any dose-response relationships.[25-28] Following single zoledronic acid doses of 1 mg, 2 mg, 4 mg, 8 mg, and 16 mg in another Phase I dose-finding study enrolling 44 patients with prostate cancer, non-small cell lung cancer, or multiple myeloma, urinary excretion of calcium, hydroxyproline, pyridinoline, deoxypyridinoline, and N-telopeptide decreased within the first week of administration at all doses. At doses of 2 mg and above, urinary markers remained suppressed for 8 weeks.[27,29]

Paget's Disease

Zoledronic acid was evaluated in a double-blind, placebo-controlled, dose-ranging study enrolling 176 patients with Paget's disease of bone. Patients received a single 1-hour infusion of zoledronic acid 50 mcg, 100 mcg, 200 mcg, or 400 mcg, or placebo. Median fasting urinary hydroxyproline and creatinine excretion were reduced in all four zoledronic acid groups, reaching a nadir by day 10. Reductions occurred sooner at the 200 and 400 mcg doses. Serum alkaline phosphatase activity also dropped, reaching a nadir by day 60 at the 50 mcg, 100 mcg, and 200 mcg doses and continued to drop at day 90 at the 400 mcg dose. All doses were more effective than placebo at day 5. The 400 mcg dose was more effective than the 50 and 100 mcg doses. At the 400 mcg dose, a 50% decline in serum alkaline phosphatase from pretreatment was observed in 46% of patients, and normalization of serum alkaline phosphatase was achieved in 20%.[30] In another dose-finding study, zoledronic acid was administered to 16 patients with Paget's disease at doses of 24 mcg, 72 mcg, 216 mcg, or 400 mcg as a single 1-hour infusion. Twenty-four hour urinary hydroxyproline/creatinine excretion was reduced by a mean of 16% to 19% from baseline on days 1, 3, 7, 10, and 14 at the 216 mcg dose and by 55% to 71% at the 400 mcg dose. Change in serum alkaline phosphatase was not observed within the 14-day follow-up period.[31]

Osteoporosis

Zoledronic acid was evaluated as a single annual injection in the treatment of postmenopausal osteoporosis in a placebo-controlled study enrolling 351 postmenopausal women with T-scores less than -2. Zoledronic acid was administered intravenously at doses of 0.25 mg, 0.5 mg, and 1 mg every 3 months, 4 mg as a single dose, and 2 mg every 6 months. After 1 year, mean bone-specific alkaline phosphatase was reduced about 40% from baseline, and median urine N-telopeptide was reduced about 50% from baseline. Changes in spinal and hipbone mineral density from baseline relative to placebo at 1 year are summarized in Table 3. Changes in bone mineral density appeared comparable regardless of the dosage regimen.[32] "Zoledronic acid infusions given at intervals of up to 1 year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis."

Table 3: Increase in Bone Mineral Density with Zoledronic Acid in Postmenopausal Osteoporosis[32]

Regimen	Spine BMD	Hip BMD
0.25 mg every 3 months x 4 doses	5.1%	3.1%
0.5 mg every 3 months x 4 doses	4.9%	3.1%
1 mg every 3 months x 4 doses	4.3%	3.2%
2 mg every 6 months x 2 doses	4.3%	3.6%
4 mg single dose	4.6%	3.3%

Contraindictions

The contraindications, warnings, and precautions for zoledronic acid are similar to those of pamidronate. Zoledronic acid is contraindicated in patients with clinical hypersensitivity to zoledronic acid monohydrate or other bisphosphonates, or any of the excipients in the injectable formulation (mannitol, sodium citrate).[1]

Warnings and Precautions

Due to the risk of renal toxicity, including renal failure, zoledronic acid doses should not exceed 4 mg and the duration of infusion should be no less than 15 minutes.[1]

In clinical trials, the risk of renal function deterioration was increased in patients who received zoledronic acid over 5 minutes compared to patients who received the same dose over 15 minutes. The risk of renal function deterioration and renal failure was also increased in patients receiving the 8 mg dose, even when it was administered over 15 minutes.[1]

For patients who have a normal serum creatinine prior to treatment, but have an increase of 0.5 mg/dL within 2 weeks of their next dose, the zoledronic acid dose should be withheld until the serum creatinine is within at least 10% of their baseline value. In patients with an abnormal serum creatinine prior to treatment who have an increase of 1 mg/dL within 2 weeks of their next dose, zoledronic acid should be withheld until the serum creatinine is within at least 10% of their baseline value.[1] Zoledronic acid should be administered with caution in patients with impaired renal function. In patients with severe renal impairment or with evidence of deterioration in renal function during zoledronic acid therapy, zoledronic acid should be administered only if the potential benefits outweigh the possible risks.[1]

Patients must be adequately rehydrated prior to the administration of zoledronic acid and throughout therapy.[1]

Administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthma patients; therefore, zoledronic acid should be used with caution in patients with aspirin-sensitive asthma.[1]

The safety and effectiveness of zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.[1]

Zoledronic acid is in Pregnancy Category C. In animal studies, administration of zoledronic acid was associated with increased pre- and post-implantation losses and stillbirths; decreased neonatal survival; skeletal, visceral, and external malformations; and adverse maternal effects including periparturient mortality. Zoledronic acid should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1]

It is not known if zoledronic acid is excreted in human milk; therefore, caution is recommended when zoledronic acid is administered to a nursing woman.[1]

The safety and effectiveness of zoledronic acid have not been established in pediatric patients.[1]

Adverse Reactions

Adverse effects have included fever, chills, bone pain, nausea, constipation, fatigue, anemia, arthralgias, myalgias, vomiting, weakness, anorexia, dyspnea, conjunctivitis, hypomagnesemia, hypocalcemia, headache, diarrhea, and hypophosphatemia.[5,6,19,22,26,27,29,30] Adverse effects were comparable in the studies comparing zoledronic acid and pamidronate (see Table 5).[6,19]

In animal studies, renal impairment occurred at lower doses of pamidronate than zoledronic acid.[3] However, in clinical trials enrolling patients with bone metastases, an increased incidence of renal adverse events was observed in patients treated with zoledronic acid 8 mg prompting discontinuation of that dose in study protocols.[24]

Drug Interactions

Loop diuretics should be used with caution in combination with zoledronic acid therapy to avoid hypocalcemia and should only be used after the patient has been adequately hydrated.[1]

Caution is recommended when bisphosphonates are administered with aminoglycosides since these agents may have an additive effect to lower serum calcium levels for a prolonged period.[1]

Table 4: Comparison of Warnings and Precautions Associated with Pamidronate and Zoledronic Acid Therapy[1,2]

Warnings/Precautions	Pamidronate	Zoledronic Acid
Warnings		
Renal toxicity	X	X
Increased serum creatinine	X	X
Hold therapy, if abnormal serum creatinine	X	X
Precautions		
Rehydration therapy prior to administration	X	X
Renal impairment	X	X
Aspirin-sensitive asthma	*	X
Safety and effectiveness in hyper calcemia associated with hyperparathyroidism unknown		X
Safety and effectiveness in hypercalcemia associated with other non-tumor-related conditions unknown		X
Pregnancy category	C	C
Breast feeding	Caution	Caution
Safety and effectiveness not established in pediatric patients	X	X
Changes in serum electrolyte levels	X	X

** = not stated in the labeling, but this problem has been reported with other bisphosphates*

Table 5: Most Common Adverse Effects Associated with the Use of Zoledronic Acid and Pamidronate in Patients Treated for Hypercalcemia of Malignancy[1]

Adverse Event	Zoledronic Acid 4 mg (n=86)	Pamidronate 90 mg (n=103)
Fever	44.2%	33%
Nausea	29.1%	27.2%
Constipation	26.7%	12.6%
Anemia	22.1%	17.5%
Dyspnea	22.1%	19.4%
Diarrhea	17.4%	16.5%
Abdominal pain	16.3%	12.6%
Progression of cancer	16.3%	20.4%
Insomnia	15.1%	9.7%
Anxiety	14%	7.8%
Urinary tract infection	14%	14.6%
Vomiting	14%	16.5%
Agitation	12.8%	7.8%
Confusion	12.8%	12.6%
Hypophosphatemia	12.8%	1.9%
Coughing	11.6%	11.7%
Hypokalemia	11.6%	15.5%
Moniliasis	11.6%	3.9%
Skeletal pain	11.6%	9.7%
Hypomagnesemia	10.5%	4.9%
Hypotension	10.5%	1.9%
Anorexia	9.3%	13.6%

Recommended Monitoring

Routine monitoring of renal function is recommended prior to every dose of zoledronic acid and periodically after each dose.[1,6] Serum calcium, electrolytes, phosphate, magnesium, and complete blood count with differential, and hematocrit/hemoglobin should also be closely monitored in patients treated with zoledronic acid.[1]

Dosing

The maximum recommended dose of zoledronic acid in hypercalcemia of malignancy is 4 mg administered as a single-dose intravenous infusion over no less than 15 minutes. Patients should be adequately rehydrated prior to administration of zoledronic acid and throughout therapy.[1]

Table 7: Comparison of Monitoring Recommendations Associated with Pamidronate and Zoledronic Acid Therapy[1,2]

Parameter	Pamidronate	Zoledronic Acid
Renal function	X	X
Serum calcium	X	X
Serum electrolytes	X	X
Serum phosphate	X	X
Serum magnesium	X	X
Complete blood count with differential	X	X
Hematocrit/hemoglobin	X	X

Retreatment with a 4 mg dose may be considered if serum calcium does not return to normal or remain normal after initial treatment. A minimum of 7 days should elapse prior to retreatment to allow for a full response to the initial dose.[1]

The zoledronic acid powder is reconstituted by adding 5 mL of Sterile Water for Injection, USP, to each vial. The resulting solution allows for the withdrawal of 4 mg of zoledronic acid. The dose must be further diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Zoledronic acid must not be mixed with calcium-containing infusion solutions, such as Lactated Ringer's solution, and should be administered in an intravenous line separate from all other medications.[1]

If not immediately administered, the solution should be stored refrigerated at 2 to 8 degrees C (36 to 46 degrees F). The total time between reconstitution, dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.[1]

Product Availability

A New Drug Application for zoledronic acid for injection was filed with the FDA in December 1999 and granted a priority review in February 2000. An approvable letter was issued in September 2000 pending complete review of additional safety data; approval was granted in August 2001.

Zoledronic acid is administered as a neutralized sodium salt formulation.[3] It is available in vials as a sterile powder for reconstitution for intravenous injection. Each vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, plus mannitol as a bulking agent and sodium citrate as a buffer.[1]

Table 6: Comparison of Drug Interactions Associated with Pamidronate and Zoledronic Acid Therapy[1,2]

Agent(s)	Pamidronate	Zoledronic acid
Loop diuretics	Commonly used combination, but increased risk of hypocalcemia – watch hydration	Commonly used combination, but increased risk of hypocalcemia – watch hydration
Aminoglycosides		*Caution*: may lower serum calcium levels with prolonged therapy

Table 8: Comparison of Dosing Associated with Pamidronate and Zoledronic Acid Therapy for the Treatment of Hypercalcemia of Malignancy[1,2]

	Pamidronate	Zoledronic Acid
Initial dose (maximum)	90 mg	4 mg
Time between doses	Minimum of 7 days	Minimum of 7 days
Route of Administration	IV	IV
Rate of administration	≥ 4 hour infusion for 60 mg dose and 24 hours for 90 mg dose	>15 minute infusion
Hydration therapy	Rehydration prior to and during therapy	Rehydration prior to and during therapy

Conclusions

Zoledronic acid appears to be a potent bisphosphonate with promising activity in the treatment of hypercalcemia of malignancy, osteolytic bone lesions, Paget's disease, and osteoporosis. Unless additional adverse effects become evident, it is likely to replace pamidronate as first-line therapy in hypercalcemia of malignancy due to its increased efficacy and shorter infusion time. Additional studies will further define its role in the treatment and prevention of metastatic bone lesions and osteoporosis.

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Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

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